Dendrimersomes: a new vesicular nanoplatform for theranostic applications

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Introduction

Dendrimersomes are a new class of nanovesicles constituted by amphiphilic Janus dendrimers.[1] Unlike other similar nanoparticles such as liposomes or polymersomes, the potential of dendrimersomes in biomedical imaging has not been explored yet. In this contribution, we report for the first time the preparation and *in vitro* characterization of dendrimersomes loaded with MRI probes. The probes were encapsulated in the aqueous core or incorporated in the bilayer through the synthesis of a novel dendrimer covalently conjugated to a Gd-complex. The ability of dendrimersomes to load drugs was also explored. Besides a preliminary *in vitro* characterization, the nanovesicles were also tested *in vivo* to assess biodistribution, blood half-time, as well as their overall imaging performance.

Methods

(3,5)12G1-PE-BMPA-G2-$(OH)_8$ dendrimer was synthesized as described elsewhere.[1] A modified synthetic procedure was followed to covalently conjugate the dendrimer to a Gd(III)-chelate (Chart 1). Dendrimersomes were prepared by using the film hydration method. Briefly, a chloroform solution of the amphiphilic molecules was dried under vacuum to obtain homogeneous films that at a later stage were hydrated at 50°C with isosmotic 300 mOsm aqueous solutions containing the clinically approved MRI agent Gadoteridol (250 mM) at pH 7.4. After the resulting suspension was purified by exhaustive dialysis, size and polydispersity index were measured by DLS. The applicability of these nanosized systems as MRI reporters was assessed by performing proton relaxometry characterization at 0.5 T and by acquiring at 298 and 310 K the Nuclear Magnetic Resonance Dispersion (NMRD) profiles describing the magnetic field dependency of the longitudinal relaxivity, r_1, over values ranging from 0.00024 to 1.65 T (corresponding to 0.01–70 MHz proton Larmor frequencies). The r_1 values of dendrimersomes made of the Gd-based Janus dendrimer were compared to equivalent nanovesicles incorporating the GdDOTAMA$(C_{18})_2$ complex, an amphiphilic Gd^{III} chelate bearing two C_{18} chains typically used for the preparation of lipid-based self assembling MRI nanoparticles. MRI experiments were carried out at 1 T and 7 T on Bruker scanners. Healthy Balb/c mice were used for biodistribution studies.

Results

Dendrimersomes composed by (3,5)12G1-PE-BMPA-G2-$(OH)_8$ only were not stable enough in isotonic buffer. However, the addition of a small amount (5 % in moles) of DSPE-PEG2000-carboxylate significantly increased the stability of the vesicles due to electrostatic repulsion. Vesicles size ranged from 150 to 200 nm (PDI < 0.2) and Gadoteridol was encapsulated in the inner core with good efficiency. Relaxometric studies showed a relatively fast water exchange across the vesicle bilayer, and a high longitudinal relaxivity was measured for the vesicles incorporated with the Gd-based dendrimer (Chart 2). Due to the high motional freedom provided by the six carbon atoms spacer (Chart 1), the relaxivity of this system was found to be slightly lower than for the vesicles incorporating the more rigid GdDOTAMA$(C_{18})_2$ complex. The *in vivo* data indicated the typical biodistribution pattern of a nanoparticle (e.g. liver and spleen accumulation) with no acute toxicity.

Conclusions

The results obtained indicate that dendrimersomes assembled from Janus dendrimers have potential to represent a new nano-platform for molecular magnetic resonance imaging experiments, particularly in the field of theranosis.

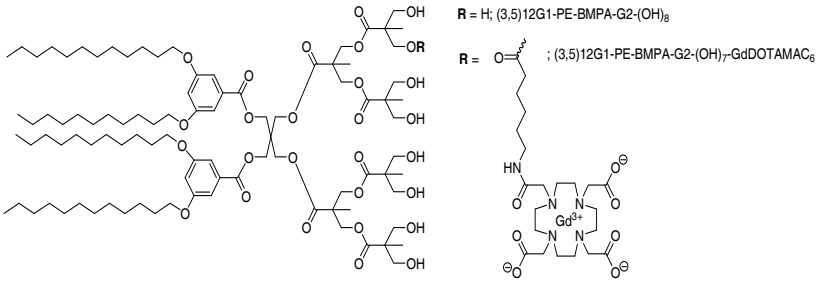

Chart 1: Janus dendrimer and its GdDOTAMAC_6 conjugate structures.

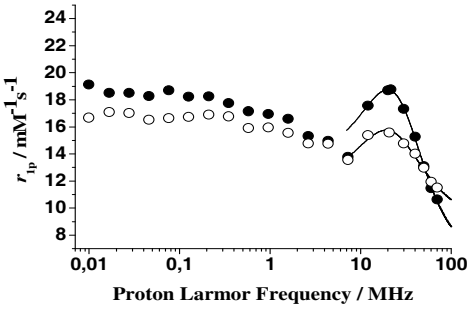

Chart 2: ^{1}H NMRD profiles of dendrimersomes incorporating GdDOTAMA$(C_{18})_2$ (●) and JD1-GdDOTAMAC_6 (○) (298 K).

Acknowledgements

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References

1. Percec V. et al., 2010, Science, 328, 1009 – 1014.